UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606**
	Master Case No. 15-2606 (RBK/JS)
	Hon. Robert B. Kugler, U.S.D.J.
	Hon. Joel Schneider, U.S.M.J.
THIS DOCUMENT RELATES TO ALL CASES	

DEFENDANTS' BRIEF IN SUPPORT OF MOTION TO EXCLUDE TESTIMONY OF SUSAN HUTFLESS, PH.D.

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TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF AUTHORITIES

Cases **Page(s)**

TABLE OF AUTHORITIES
(continued)

Page

Statutes

Other Authorities

TABLE OF AUTHORITIES
(continued)

Page

TABLE OF AUTHORITIES
(continued)

Page

PRELIMINARY STATEMENT

Plaintiffs proffer Dr. Susan Hutfless, an epidemiologist, for the opinion that medications containing olmesartan medoxomil ("olmesartan") cause sprue-like enteropathy. Dr. Hutfless claims to follow well-established methodologies for reaching opinions on general causation. But this is merely window-dressing, as her general causation opinion is based on eight spontaneously reported adverse events submitted to Daiichi Sankyo, Inc. ("DSI") between 2004 and 2006. Basing a general causation opinion on eight non-peer-reviewed adverse event reports is contrary to well-established scientific methodology for establishing general causation.

Even assuming Dr. Hutfless had not based her opinion on eight adverse events reports, her general causation opinion remains inadmissible because she is quick to abandon scientific principles and methodology when it suits her. To that end, Dr. Hutfless asserts that she conducted a Cochrane systematic review of the data and applied the well-established Bradford-Hill factors to arrive at an opinion on general causation. This would be a sound methodology if appropriately applied by Dr. Hutfless. However, Dr. Hutfless simply did not do this.

Indeed, there are numerous ways in which Dr. Hutfless failed to use proper scientific methods to reach her conclusions:

1. Dr. Hutfless could not define sprue-like enteropathy. Nevertheless,

she purports to reach a conclusion concerning the causal relationship between olmesartan and sprue-like enteropathy, an entity she admits she cannot define.

2. Dr. Hutfless based her general causation opinion on eight MedWatch adverse event reports ("MedWatch reports") submitted by users of olmesartan between 2004 and 2006. Thus, Dr. Hutfless concluded that a causal relationship between olmesartan and sprue-like enteropathy was established in 2006 – a full six years before the Mayo Clinic first introduced the concept of sprue-like enteropathy.

3. Dr. Hutfless could not explain the methodology by which the set of MedWatch reports on which she relied were selected. Dr. Hutfless initially claimed to have developed search terms that generated 335 MedWatch reports from 12,127 reports produced by DSI in discovery. After months of abstracting data from these 335 reports and less than a month before finalizing her expert report, her methodology changed. At some point in November 2016, Dr. Daniel Leffler – another plaintiffs' expert – revised her search terms in a way that she could not explain. The revision of search terms reduced the number of MedWatch reports from 335 to 60. Dr. Hutfless's conclusion that the eight MedWatch reports (which are included in the pared down group of 60) "prove" general causation was based on Dr. Leffler's assurances that each of the eight MedWatch reports were cases of "olmesartan induced enteropathy." She concluded as such without

performing an independent assessment of the MedWatch reports.

4. Dr. Hutfless's application of the WHO causality framework, which is used to assess causality for individual adverse events, was unsound. At Dr. Leffler's direction, she assumed patients lacked other comorbidities, allergies, and/or the presence of other medications when such information was missing or not identified in the MedWatch reports she reviewed. So, even though information on a patient's comorbidities, allergies, or other medications was not specified in a number of the MedWatch reports, Dr. Hutfless blindly assumed that there were no such alternative causes that could explain the symptoms. Based on these unsupported assumptions, she determined that the eight MedWatch reports on which she relied merited a WHO ranking of "probable/likely" or "certain" for causality.

5. For her general causation opinions, Dr. Hutfless disregarded a number of randomized clinical trials studying olmesartan that did not report any imbalance in gastrointestinal adverse events. Her reasoning was that the absence of an adverse event does not mean that none occurred. But this "approach" was inconsistent with her treatment of the MedWatch reports on which she relied, a number of which were missing information about comorbidities and other medications. With these MedWatch reports, Dr. Hutfless concluded that the patient had not suffered from any co-morbidities or used medications that might explain

the appearance of enteropathy or its resolution.

6. Dr. Hutfless cherry-picked the epidemiological data by ignoring certain studies and concluding that others – which failed to find an association between olmesartan and sprue-like enteropathy – "did not contribute to the evidence." Similarly, with other studies not supportive of her conclusions, she decided that they "did not contribute to the evidence" because the stated endpoint was not "olmesartan induced enteropathy." In contrast, she relied heavily on one epidemiologic study, even though it did not specifically analyze "olmesartan induced enteropathy" or control for other drug use that could explain the symptoms of malabsorption – the study's stated endpoint. Further, she embraced the data from this study even though it generated a statistically significant finding of an increased risk for celiac disease, a condition Dr. Hutfless admits is not caused by olmesartan.

7. Dr. Hutfless relied on a mechanistic paper that was directly contradicted by an earlier paper written by the same group of authors. Dr. Hutfless's analysis did not address the earlier paper, and she did not offer any explanation for ignoring the conclusion of that earlier study.

8. Dr. Hutfless scored the published case reports of sprue-like enteropathy ("case reports") using the WHO system as "Probable/Likely." To arrive at this score, she made unjustified assumptions based on the case reports

having been peer-reviewed. According to Dr. Hutfless, no alternative explanations existed (such as co-morbidities or other medications) for these so-called sprue-like enteropathy cases because the journals would not have published them if there were alternative explanations for the symptoms. She did not, however, determine if this was true when reviewing the case reports.

These, and other fundamental shortcoming described below, demonstrate that Dr. Hutfless's methodology is unsound and inadmissible under *Daubert*. Her general causation opinion should therefore be excluded in its entirety.

STATEMENT OF FACTS

I. The Claimed Event

This MDL was created for products liability cases for claims by plaintiffs who have taken olmesartan-containing products and allege that as a result they sustained "serious gastrointestinal injury, including sprue-like enteropathy, lymphocytic colitis, microscopic colitis, and collagenous colitis." *See In re: Benicar (Olmesartan) Products Liability Litigation*, MDL No. 2606, 2015 U.S. Dist. LEXIS 44047 (JPML Apr. 3, 2015).

II. The Claimed Injury: Identification, Description, and Diagnosis

The litigation was inspired by a June 25, 2012 publication reporting "a unique case series" involving "a novel association between severe sprue-like enteropathy and olmesartan [the active ingredient in the Benicar® products.]"

Rubio-Tapia A. et al., Severe Sprue-like Enteropathy Associated with olmesartan. *See* Exhibit C to the Certification of Daniel B. Carroll, Esq. ("Carroll Cert."), Alberto Rubio-Tapia, et al. *Severe Spruelike Enteropathy Associated With Olmesartan*, Mayo Clin Proc. 732, 738 (2012) ("Mayo Clinic paper"). As stated by the authors of the article, the case series "lacks all the information necessary to prove causality but rather reflects an association." *Id.* at 735.

Enteropathy refers to injury to the small bowel. There are many causes of enteropathy including celiac disease, tropical sprue, collagenous sprue, small intestinal bacterial overgrowth, autoimmune enteropathy, and idiopathic enteropathy. "Sprue-like enteropathy associated with olmesartan" was described by the Mayo Clinic in their June 2012 paper as a "novel" clinical entity based on a "unique" case series. *Id.* at 738. The senior author of the publication, Dr. Joseph A. Murray, has a number of YouTube presentations on the paper, and was deposed in one of these cases, where he repeatedly took the position that sprue-like enteropathy is rare and a new syndrome – previously unreported in medical literature in association with ARB medications – and that patients doing well on olmesartan medications should not discontinue them. *See* Mayo Proceedings, *Severe Sprue-like Enteropathy Associated with Olmesartan*, YouTube, (Oct. 15, 2012), http://www.youtube.com/watch?v=CmrZBeikR-Y; *see also* Mayo Clinic, *Examining Sprue-like Symptoms Associated with Olmesartan*, YouTube (July 11,

2014), http://www.youtube.com/watch?v=y5n2Nd5A-_A.

The clinical and pathologic features of sprue-like enteropathy are severe, chronic diarrhea with substantial weight loss, vomiting, and villous atrophy. Intestinal villi are small, finger-like projections that protrude from the epithelial lining of the small intestinal wall; there are no villi in the stomach or large intestine/colon. Villi increase the internal surface area of the small intestinal wall available for absorption. If the intestinal villi are inflamed or destroyed by pathogens or an abnormal autoimmune reaction, the absorption of nutrients may be disrupted with resulting malabsorption. Villous atrophy is a non-specific finding and is seen in a number of common conditions including, but not limited to, celiac disease, a common hereditary auto-immune disease.

The scientists from the Mayo Clinic stated in 2012 that diagnosing sprue-like enteropathy associated with olmesartan requires that clinicians eliminate other causes of enteropathy (such as NSAIDs, etc.) and demonstrate complete clinical resolution of the patient's symptoms after olmesartan withdrawal. *See, e.g.*, Carroll Cert., Exhibit C, Alberto Rubio-Tapia, et al. *Severe Spruelike Enteropathy Associated With Olmesartan,* Mayo Clin Proc. 2012; 87(8):732-738, at 737, Table 3 (identifying clinical features of sprue-like enteropathy and requiring exclusion of celiac disease); Carroll Cert., Exhibit D, Isabel A. Hujoel & Alberto Rubio-Tapia, *Sprue-like Enteropathy Associated with Olmesartan: A New Kid on the*

Enteropathy Block, GE Port J Gastroenterol. 2016;23(2):61-65 (speaking about confirmation of a diagnosis). This would include ruling out the following other disease entities: Refractory celiac disease; Tropical sprue; Collagenous sprue; Lactose and fructose intolerance; Giardiasis, a parasitic disease; Small intestinal bacterial overgrowth; Pancreatic insufficiency; Functional bowel disorders; Malignancies; Microscopic colitis, and Protein-losing enteropathy.

To further complicate the diagnostic process for sprue-like enteropathy, a physician needs to consider whether the patient, despite taking olmesartan, is afflicted with idiopathic enteropathy. Idiopathic enteropathy involves clinical symptoms that are virtually indistinguishable from sprue-like enteropathy. As plaintiffs' experts have admitted, a person taking olmesartan can develop idiopathic enteropathy for similar reasons to patients who do not take olmesartan. *See, e.g.*, Carroll Cert., Exhibit E, Deposition of Dr. Stephen Lagana at 140:12-143:6. Indeed, there are cases of idiopathic enteropathy where olmesartan may be an "innocent bystander . . . ." *See* Carroll Cert., Exhibit F, Aziz I., et al., The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-2015), GUT, 1–10 (2016) .

III. Dr. Hutfless's Review

A. Dr. Hutfless's Reliance on Bradford Hill Factors and the Cochrane Collaborative

Dr. Hutfless claims she utilized the Bradford Hill criteria to examine the relationship between olmesartan and sprue-like enteropathy. *See* Carroll Cert., Exhibit A, Report of Susan Hutfless, Ph.D. ("Hutfless Rep.") at 15-16 (describing the Bradford-Hill criteria as a "commonly used and generally accepted" methodology for assessing causality and proclaiming her application of the criteria to this evidence); *see also* Carroll Cert., Exhibit B, Deposition of Susan Hutfless ("Hutfless Dep.") at 161:5-162:2. Dr. Hutfless also declared that her opinions are the product of a "systematic review" of the evidence in accordance with the principles of the Cochrane Collaboration. Part of doing a Cochrane review is assessing the quality of individual studies for inclusion in the review. *Id.* at 370:23-371:5.

The Cochrane Collaboration has produced the Cochrane Handbook for Systematic Reviews of Interventions ("Cochrane Handbook"). The Cochrane Handbook describes the "quality" of different types of evidence, assigning quality ratings to each type. Of note, Table 12.2.a – excerpted below – assigned a quality rating of "very low" to case series/case reports. *See* Holger J. Schunemann, et al., *Interpreting results and drawing conclusions, in* Cochrane Handbook for Systematic Reviews of Interventions 359-387; 361 (J. Higgins & S. Green 2008).

Table 12.2.a Levels of quality of a body of evidence in the GRADE approach

Underlying methodology	Quality rating
Randomized trials; or double-upgraded observational studies.	High
Downgraded randomized trials; or upgraded observational studies.	Moderate
Double-downgraded randomized trials; or observational studies.	Low
Triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.	Very low

Dr. Hutfless acknowledged her use and acceptance of the Cochrane "GRADE approach" in prior analyses of "exposure outcome relationships." Carroll Cert., Exhibit B, Hutfless Dep. at 233:9-22. She also admitted that this Cochrane approach assigned a quality rating of "very low" to case report evidence. *Id.* at 235:9-17. However, as discussed below, Dr. Hutfless elevates the adverse events reports above all other forms of evidence in reaching her general causation opinion in this case.

LEGAL ARGUMENT

In determining whether the general causation opinion of an expert like Dr. Hutfless is based on a reliable methodology, the Court must look to: "whether the expert relied on epidemiological studies; whether the expert ignored or sufficiently addressed epidemiological studies which contradicted his hypothesis, explaining the discrepancy between his hypothesis and that of the authors; and, whether the findings set forth in the studies are statistically significant." *Pritchard v. Dow Agro Scis.*, 705 F. Supp. 2d 471, 484-85 (W.D. Pa. 2010) (relying on *Heller v. Shaw*

Indus., Inc., 167 F.3d 146 (3d Cir. 1999)). In the absence of epidemiological studies supporting general causation, "an expert [only] offers a reliable causation opinion through the use of some other valid scientific methodology." *Id.* at 485.

Scientists recognize a hierarchy of evidence as a "fundamental principle of evidence-based medicine":

> A fundamental principle of evidence-based medicine . . . is that the strength of medical evidence supporting a theory or strategy is hierarchical. When ordered from strongest to weakest, systematic review of randomized trials (meta-analysis) is at the top, followed by single randomized trials, systematic reviews of observational studies, single observational studies, physiological studies, and unsystematic clinical observations. An analysis of the frequency with which various study designs are cited by others provides empirical evidence supporting the influence of meta-analysis followed by randomized controlled trials in the medical hierarchy. Although they are at the bottom of the evidence hierarchy, unsystematic clinical observations or case reports may be the first signals of adverse events or associations that are later confirmed with larger or controlled epidemiological studies. . . . Nonetheless, subsequent studies may not confirm initial reports. . . .

REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 723-24. The consensus within the scientific community is that epidemiology—which examines patterns in exposed and unexposed populations—is at the top of this evidence hierarchy, and adverse events and case reports "reflect only reported data, not scientific methodology" and "pale in comparison" to epidemiological studies. *In re Zoloft (Sertraline Hydrocloride) Prod. Liab. Litig.*, 176 F. Supp. 3d 483, 497 (E.D. Pa. 2016) (internal citations omitted).; *see also Carl v. Johnson & Johnson*, No. 300 (MCL),

slip op. at 12-17 (N.J. Super. Ct. Law Div. Sept. 2, 2016), appeal pending attached at Carroll Cert., Exhibit DD.

I. Dr. Hutfless's general causation opinion is inadmissible under *Daubert* because the scientific "methodology" she claims to have used is not the basis for her opinion.

A. As a threshold matter, Dr. Hutfless's entire opinion about general causation is undermined by her inability to define the condition that she claims olmesartan causes.

Dr. Hutfless opines that the evidence proves olmesartan causes sprue-like enteropathy, while also oddly admitting that she cannot define sprue-like enteropathy. Dr. Hutfless defined sprue-like enteropathy in a circular manner as "the constellation of symptoms consistent with Olmesartan induced enteropathy . . . ." Carroll Cert., Exhibit B, Hutfless Dep., at 160:20-23, 166:15-23.

When pressed to define the condition she allegedly studied, Dr. Hutfless stated that she "relied upon a clinician [plaintiffs' expert, Dr. Daniel Leffler] to come to the assessment of the olmesartan-induced enteropathy cases." *Id.* 182:14-18. In other words, she did not develop any definition of the condition for purposes of her general causation analysis. *Id.* 174:11-14. Nor could she list the diagnostic criteria for sprue-like enteropathy as reported in the literature, stating instead that she is "not a clinician" and "do[es] not make diagnoses." *Id.* 178:12-14. When asked how she "ruled out" other potential causes of enteropathy when assessing symptoms of "olmesartan induced enteropathy" discussed in the

published case reports, Dr. Hutfless responded that she simply accepted the authors' assessment of those cases. In fact, she stated that "[i]f the clinician considers the case to be olmesartan-induced enteropathy, it is a case of olmesartan-induced enteropathy." *Id.* 183:14-18, 193:12-194:1.

By failing to provide clearly-defined parameters and a definition of the symptoms and histology for sprue-like enteropathy, Dr. Hutfless could not possibly conduct an appropriate review of the data. Being able to define sprue-like enteropathy is critically important, because it is impossible to determine in a scientifically reliable manner what data are relevant to the relevant outcome if the outcome itself is not defined.

B. Dr. Hutfless's general causation opinion is based on a review of eight MedWatch reports, not on a valid scientific methodology.

Dr. Hutfless's report offers the results of a data mining exercise of the FAERS database, a purported review of 60 MedWatch reports, and a review of published case reports in support of her opinions. But her report also concedes that none of these data – even if properly utilized in a Cochrane systematic review or assessment of the Bradford Hill factors – actually formed the basis of her causation opinion. Dr. Hutfless stated in her report: "It is my opinion, to a reasonable degree of scientific certainty, that there is sufficient evidence to establish a causal relationship between olmesartan and enteropathy. There is consistent evidence from the MedWatch case reports and signals from the FAERS that this causal

association was established in 2006." Carroll Cert., Exhibit A, Hutfless Rep., at 6. In essence, Dr. Hutfless bases her general causation opinion *entirely* on eight MedWatch reports dated between 2004 and 2006. Carroll Cert., Exhibit B, Hutfless Dep. at 416:14-417:2.

Dr. Hutfless's reliance on these eight MedWatch reports is fundamentally at odds with performing a Cochrane systematic review. Published case reports and spontaneous adverse events reside at the bottom of the hierarchy of scientific evidence used to assess general causation. These reports simply reflect what a submitter notes with respect to a temporal relationship between a drug's relationship and an unexpected physical reaction. *See Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 537-38 (W.D. Pa. 2003). Adverse drug reactions "have been rejected as reliable scientific evidence supporting expert opinion so as to meet the requirements set forth in *Daubert*." *Id.* (citing *Jones v. United States*, 933 F. Supp. 894, 899 (N.D. Cal. 1996), *aff'd* 127 F.3d 1154 (9th Cir. 1997) (anecdotal case reports are not derived through the scientific method and 'fall short of the proven, cause and effect relationship that is necessary to satisfy the *Daubert* standard.'"); *Sanderson v. Int'l Flavors*, 950 F. Supp. 981, 1000 (C.D. Cal. 1996) (holding that temporal coincidence is not a "valid scientific connection" to satisfy *Daubert*); *Casey v. Ohio Med. Prods.*, 877 F. Supp. 1380, 1385-86 (N.D. Cal. 1995) (case reports are not reliable evidence of causation and not sufficiently based

on scientific reliability and methodology to be admitted into evidence under Fed. R. Evid. 702 and 703)). "[C]ase reports raise questions; they do not answer them." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1254 (11th Cir. 2005).

The Third Circuit requires that experts who rely on case studies demonstrate a reliable association between exposure and the alleged injury. *See Pritchard*, 705 F. Supp. 2d at 484-87. "Moreover, it is the Plaintiffs' burden to demonstrate that [the expert's opinion premised on case studies] is based on 'good grounds' and not the Defendants' burden to refute the same." *Id.* Dr. Hutfless demonstrates no such reliable association.

The FDA also acknowledges that adverse event reports are not to be taken as evidence that exposure to a chemical *caused* the condition alleged in the reports. On its FAERS webpage, the FDA states plainly the limitations of adverse event reports in determining causation in individual cases, much less general causation.

> Do FAERS Data Have Limitations?
>
> FAERS data do have limitations. First, there is no certainty that the reported event (adverse event or medication error) was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Carroll Cert., Exhibit G, FOOD AND DRUG ADMIN., QUESTIONS AND ANSWERS ON FDA'S ADVERSE EVENT REPORTING SYSTEM (FAERS), (last updated May 5, 2016), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/.

Thus, Dr. Hutfless's reliance on eight MedWatch reports to establish general causation is a clear departure from reliable scientific methodology.

C. The poorly defined process by which the MedWatch reports on which Dr. Hutfless relies were selected further establishes that her supposed methodology is not scientifically valid.

Another significant weakness in Dr. Hutfless's opinion is the selection of the MedWatch reports she ultimately used in her analysis. DSI produced 12,127 adverse event reports using search terms selected by the plaintiffs in purported collaboration with their experts. Carroll Cert., Exhibit H, Transcript of Sept. 30, 2015 Hearing, T16:10-17:14. Dr. Hutfless testified that she drafted a list of "symptoms that were relevant" to symptoms of sprue-like enteropathy based on her review of the literature and conversations with Dr. Leffler, which resulted in a group of 335 MedWatch reports. Carroll Cert., Exhibit B, Hutfless Dep. at 52:10-54:9. But she could not specifically recall what search terms she used to generate the 335 reports. *Id.* 55:11-57:3 (she thinks the terms "were related" to diarrhea, celiac disease, etc. and included cases demonstrating de-challenge); *see also id.* 65:7-66:2. In May 2016, Dr. Hutfless and her associates began abstracting

information from the 335 MedWatch reports to include in a database for further analysis. *Id.* at 107:5-11.

Sometime thereafter, Dr. Leffler and his associates began to evaluate each of the 335 reports using a ten-point scale for assessing individual causality, known as the Naranjo causality scale. *Id.* 135:22-136:4. The Naranjo causality scale was designed as a "simple method to assess the causality of [adverse drug reactions]" in different clinical and case scenarios. Carroll Cert., Exhibit I, C.A. Naranjo, M.D., et al. *A method for estimating the probability of estimating the probability of adverse drug reactions.* Clin. Pharmacol. Ther. 239-45: 240; Aug. 1981. Dr. Hutfless's use of such a scale to reach general causation opinions is not the purpose for such frameworks. *Rhodes v. Bayer Healthcare Pharms., Inc.*, No. 10-1695, 2013 WL 1289050, at *6 (W.D. La. Mar. 26, 2013), Carroll Cert. Exhibit EE. Scales such as Naranjo are generally "a classification system, not a method used to determine actual causal relationships and/or causal assessments." *Id.* (citing Taofikat B. Agbabiaka, *Methods for Causality Assessment of Adverse Drug Reactions: A Systematic Review*, 31(1) Drug Safety 21, 28-29 (2008)). Thus, reliance on such causality assessment tools to determine general causation is an unreliable method. *Id.*

The WHO-UMC assessment framework was developed as an alternative framework to Naranjo. Carroll Cert., Exhibit J, WHO-UMC Causality Scale at 1.

This assessment lists "causality categories," including "certain," "probable/likely," "possible," "unlikely," "conditional/unclassified," and "unassessable/ unclassifiable." *Id.* at Table 2. To the extent that tools such as the Naranjo scale and WHO-UMC framework are used, they must be employed consistent with their purpose. *See Howley v. Experian Info. Solutions, Inc.*, 813 F. Supp. 2d 629, 640 n.7 (D.N.J. 2011). However, Dr. Hutfless failed to do so here.

Dr. Hutfless began by asking Dr. Leffler to apply the Naranjo causality scale. To categorize an adverse drug reaction under the Naranjo scale, one uses a series of ten questions, for which a "yes," "no," or "do not know" response should be given. Carroll Cert., Exhibit I, Naranjo at Table I. One of the questions is whether there are "alternative causes (other than the drug) that could on their own have caused the reaction?" *Id.* The problem for Dr. Hutfless was that many of the 335 MedWatch reports did not contain sufficient information from which to assess if co-morbidities or other drug use might explain the symptoms. Without affirmative evidence, the scorer could not award points by answering "no" to such questions – which ultimately would affect the total score awarded for each MedWatch report on the Naranjo scale.

According to Dr. Hutfless, Dr. Leffler and she had a "deeper discussion" about the Naranjo scale and how "well" it would apply to sprue-like enteropathy. Hutfless Dep., Exhibit B, 130:4-131:17. This "deeper discussion" ultimately led

to: (1) the re-definition of the search terms in a way that pared down the results from 335 to 60 MedWatch reports, and (2) Dr. Hutfless and Dr. Leffler changing their answer(s) in the Naranjo scale to "no" for comorbidities, allergies, and medications *any time that this information was missing or not mentioned in a particular MedWatch report*. *Id.* 156:20-157:2 ("Based on our conversation any time something was listed as missing or not mentioned it was no. The reason why is there were so many of these where the comorbidities effect, medications effect, and allergies effect was a no in his mind."). So, although information on a patient's comorbidities, allergies, or other medications was not specified in a particular MedWatch report(s), Dr. Hutfless blindly assumed for a number of the cases that there were no alternative causes other than olmesartan that could explain the symptoms:

> Q. If there's no information provided in the MedWatch report about whether a patient was using other drugs that might explain the reaction and no information is given about other comorbidities, you didn't score this as not mentioned. You said no, negative, there were no other comorbidities, there were no other possible drugs that might have influenced or might be explaining the effect.
>
> ***
>
> A. . . . Dr. Leffler, to my understanding, also had source files which I believe is notes or other sources or something like that, that goes along with the MedWatch forms. I've never seen the source files. I have a superficial understanding of what the content of information that was there, based on what he was actually able to review. But he used the content in the MedWatch form as well as those source files to come to a determination of no -- to come to a determination that

anytime it said not mentioned or missing, that was in fact a no.

Id. 158:2-160:9.

Dr. Hutfless could not explain how Dr. Leffler pared down the initial cohort of 335 MedWatch reports to just 60 and, thus, it is entirely unclear whether the 60 MedWatch reports were representative of the larger collection of MedWatch reports. In addition, there was no need to further score the 60 reports as they had been doing for the 335, because Dr. Leffler assured Dr. Hutfless that each of the 60 reports were cases of "olmesartan induced enteropathy." Dr. Hutfless did not question Dr. Leffler about his methodology or conclusion, stating instead that she trusted "his clinical judgment." *Id.* 422:6-424:8; *see also id.* 68:24-71:14, 105:12-17 ("Dan's [Leffler] exact process of coming up with those list of terms for his list of 60 cases which he identified, he came up with those on his own using his clinical judgment for that particular list for the 60 . . . ."), 174:18-20 ("I relied upon Dr. Leffler's assessment . . . .").

Dr. Hutfless's "failure to assess the validity of the experts [s]he relied upon together with [her] unblinking reliance on those experts' opinions, demonstrates that the methodology [s[he used to formulate [her] opinion was flawed under Daubert as it was not calculated to produce reliable results." *See In re TMI Litig.*, 193 F.3d 613, 716 (3d Cir. 1999). In *TMI*, one of the plaintiffs' experts relied upon the opinions of other plaintiffs' experts. *Id.* at 714-15. Specifically, the expert

testified that he left it up to other experts to determine key facts related to his opinion. *Id.* The Court described the expert's opinion as "somewhat analogous to the last domino in the line that begins to fall when the first domino is toppled." *Id.* at 715. The expert also admitted that he never attempted to assess the validity of the assumptions on which he relied. *Id.* For those reasons, the Court affirmed the trial court's decision to exclude the expert's testimony. *Id.* at 716.

The same is true here of Dr. Hutfless's opinions. As demonstrated above, she relied upon Dr. Leffler's opinion as to which of the adverse event reports represented sprue-like enteropathy cases. Dr. Hutfless's general causation opinion, using those adverse event reports, is wholly dependent upon Dr. Leffler's determination of which reports show sprue-like enteropathy. Therefore, by assuming Dr. Leffler's determinations were correct, Dr. Hutfless "assumed the very matter at issue on which [s]he was called to express [her] opinion." *See TK-7 Corp. v. Estate of Barbouti*, 993 F.2d 722, 732 (10th Cir. 1993). Dr. Hutfless's use of these assumptions thus fails to meet the requirements of Rule 703 and Daubert. *Id.*

Even still, the mystery surrounding the set of 60 MedWatch reports is not limited to Dr. Hutfless. Two of plaintiffs' other experts, Drs. Leffler and Kessler, also relied on them (or in the case of Dr. Hutfless, a small subset of them) in support of their opinions. *See* Carroll Cert., Exhibit A, Hutfless Rep. at 17; Exhibit

K, Report of Daniel Leffler, M.D., at 14; Exhibit L, Report of David Kessler, at ¶¶80-81. But none of these three experts could consistently describe how or when these 60 MedWatch reports of "sprue-like enteropathy" were identified from the larger set of reports produced by DSI. All of their accounts are conflicting:

- **Dr. Hutfless:** Dr. Hutfless claims she developed a list of terms for plaintiffs' counsel to run searches in the MedWatch reports produced by DSI, a list that generated 335 reports. She does not know precisely how or when Dr. Leffler pared down the 335 reports to 60. *See* Carroll Cert., Exhibit B, Hutfless Dep. at 50:12-53:22, 104:13-105:17, 112:5-114:23;

- **Dr. Leffler**: Dr. Leffler did not have any input on the selection criteria for the 62 MedWatch reports, and did not know how Dr. Kessler searched the 9,540 MedWatch reports produced by DSI. *See* Carroll Cert., Exhibit M, Deposition of Daniel Leffler, M.D. at 198:5-16, 198:19, 199:8-18;

- **Dr. Kessler**: Dr. Kessler claimed to have generated and provided the list of search terms to plaintiffs' counsel, who performed the search. He recalls seeking Dr. Leffler's approval of the terms, and Dr. Leffler agreed that this list of search terms (i.e., symptoms) were "relevant criteria." This search generated a list of 62 MedWatch reports that matched the symptoms Dr. Kessler associated with olmesartan enteropathy. *See* Carroll Cert., Exhibit N Deposition of David Kessler, M.D. at 196:17-199:6.

Without a clear understanding of how these 60 MedWatch reports were selected, it is impossible to know what criteria was used to generate the list and whether that criteria was over-inclusive or under-inclusive. Such a methodology is not scientifically sound.

D. The manner in which Dr. Hutfless analyzed the MedWatch forms is inconsistent with the manner in which she analyzed other evidence, further revealing the unreliability of the "methodology" supporting her opinion.

As discussed more fully *infra* at page 34, Dr. Hutfless concluded that the randomized clinical trials were not relevant to her assessment because "the absence of reported cases of celiac disease from the published trials does not provide evidence that there is no causal relationship between olmesartan-containing products and olmesartan-induced enteropathy." Carroll Cert., Exhibit A, Hutfless Rep., at 28. On the other hand, Dr. Hutfless assumed that a MedWatch report without information on a patient's co-morbidities or concomitant medications could explain the origin of enteropathy. Thus, Dr. Hutfless's methodology was fundamentally inconsistent with respect to how she treated the results of randomized clinical trials compared to the spontaneous adverse events reflected in MedWatch reports.

Another example of Dr. Hutfless's result-driven methodology is how she used the WHO definition of the "Certain" and "Probable/Likely" categories. To categorize the causality of a case report as "Probable/Likely," one must

affirmatively show that "it is unlikely that the symptoms at issue can be attributed to disease or other drugs". Carroll Cert., Exhibit J, WHO-UMC Causality Scale, at Table 2. For a "Certain" determination, the symptoms "cannot be explained by disease or other drugs." *Id.* While Dr. Hutfless initially stated that 90% of the MedWatch reports (54 of 60) were assessed as "Certain" or "Probably/Likely" related to olmesartan (Carroll Cert., Exhibit A, Hutfless Rep. at 17), she later acknowledged that 55 of the 60 MedWatch reports either had other potential alternative causes identified when the Naranjo scale was applied or lacked information on this question. Exhibit B, Hutfless Dep. at 130:4-134:19.

Additionally, for 52 of the 60 MedWatch reports, Dr. Hutfless "assumed" (based on Dr. Leffler's recommendation) that information concerning other drugs, comorbidities, and allergies had no effect on the patient's symptoms – despite the fact that this information was missing or not mentioned in the forms. *See id.* 158:2-160:9; *see also* Carroll Cert., Exhibit O, 11/23/2016 E-mail chain between S. Hutfless and D. Leffler. Dr. Hutfless's application of the WHO causality assessment was methodologically deficient due to her failure to account for the potential relationship between other drugs and/or disease and the symptoms described in the MedWatch reports identified in her report.

All eight of MedWatch reports that Dr. Hutfless ultimately relies on are missing information on other medications and/or make reference to other potential

alternative causes. In fact, according to documents produced after Dr. Hutfless's deposition, Dr. Leffler's team determined – using the Naranjo scale – that seven of these eight reports contained possible alternative causes that could cause the symptoms. *See* Carroll Cert., Exhibit P, Naranjo Score Assessments for 8 MedWatch reports. Consequently, none of these reports should have been scored as "Probable/Likely," much less "Certain," under the WHO causality assessment:

- **SU-2004-002638**: Patient was diagnosed with Giardia, an intestinal infection caused by a water-borne parasite, after developing diarrhea.
- **SU-2005-004027:** Patient was diagnosed with celiac disease. No information about the patient's adherence to a gluten-free diet was included in the report.
- **SP-2006-003299:** Concomitant medications "[n]ot reported."
- **SP-2006-003369:** In the Naranjo score sheets produced following Dr. Hutfless's deposition, the response was "yes" in answer to the question on whether alternative causes could have produced the reaction.
- **SU-2006-005001:** Patient diagnosed with celiac disease. The report noted that the patient's celiac disease symptoms had "vastly improved with diet."
- **SU-2006-005321:** Report notes that "[n]o other information was provided [for] past medical history, concomitant medications or event status/outcome."

- **SU-2006-005527:** Patient was diagnosed with tropical sprue after traveling to the Caribbean. The report also noted that, after discontinuing olmesartan, the "events of Tropical sprue, vomiting, and diarrhea have not abated."
- **SU-2006-005596:** Patient was diagnosed with celiac disease. In the Naranjo score sheets produced following Dr. Hutfless's deposition, the response was "yes" in answer to the question on whether alternative causes could have produced the reaction.

See Carroll Cert., Exhibit Q, 8 MedWatch Forms; Carroll Cert., Exhibit P, Naranjo Score Assessments for 8 MedWatch reports.

Despite the missing information, Dr. Hutfless concluded that these MedWatch reports prove general causation. Although spending weeks attempting to score the reports using the Naranjo and later the WHO criteria, Dr. Hutfless ultimately abandoned any pretense of using accepted frameworks for scoring individual cases and simply accepted Dr. Leffler's assurance that all eight were cases of "olmesartan induced enteropathy." Hutfless Dep., Exhibit B, 174:5-10 ("[T]he determination of which of these were cases of olmesartan induced enteropathy was decided by Dr. Leffler, based on his expert opinion."), 422:6-424:12. The "score" sheet Dr. Hutfless produced at her deposition confirmed that her collaboration with Dr. Leffler resulted in a score of "Probable/Likely" or "Certain" for the eight MedWatch cases only by assuming there were no co-

morbidities or other medications used that could explain the symptoms. *See* Carroll Cert., Exhibit R, "Score" Sheet, exhibit 44 to Hutfless Dep.

Finally, Dr. Hutfless stated in her report that she identified a total of 162 cases of sprue-like enteropathy in the published case report literature. Carroll Cert., Exhibit A, Hutfless Rep. at 22 (describing 162 cases allegedly reporting a positive de-challenge). She concluded that those cases merited a "WHO causality assessment of probable for the majority of cases (temporality plus de-challenge)." *Id.* at 22. To arrive at this score, she made unjustified assumptions based on the case reports having been peer-reviewed. Specifically, Dr. Hutfless assumed no alternative explanations existed (such as co-morbidities or other medications) for these so-called sprue-like enteropathy cases because the journals would not have published the case reports if they did not meet the WHO criteria. *See* Carroll Cert., Exhibit B, Hutfless Dep. at 448:19-450:19. She did not, however, determine if this was true when reviewing the case reports. *See id.*

Ignoring the possibility of potential alternative causes in her WHO causality analysis further demonstrates the unscientific approach Dr. Hutfless took to analyzing general causation.

II. Dr. Hutfless's general causation opinion also is inadmissible under *Daubert* because she did not properly apply the Bradford-Hill factors.

"In determining whether an observed association between a chemical and a disease is causal (*i.e.*, general causation), scientists are guided by various factors,

which are often referred to as the Hill criteria." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 592–93 (D.N.J. 2002), *aff'd*, 68 F. App'x 356 (3d Cir. 2003). Bradford–Hill criteria "have been recognized for decades as a generally accepted methodological approach for determining causation in tort cases involving toxic exposure." *In re Zoloft (Sertraline Hydrocloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 466, 480 (E.D. Pa. 2014). "While an expert need not consider or satisfy every criteria in order to reach a reliable causation opinion," expert opinions should be excluded where an expert fails to consider the Bradford-Hill criteria as a whole. *In re Zoloft*, 26 F. Supp. 3d at 480. "The Court cannot allow unscientific speculation to be offered, even by genuinely talented scientists." *Id.* at 481.

Dr. Hutfless claims she used the Bradford-Hill factors to examine the relationship between olmesartan and sprue-like enteropathy. *See* Carroll Cert., Exhibit A, Hutfless Rep., at 15-16 (describing the Bradford-Hill factors as a "commonly used and generally accepted" methodology for assessing causality and proclaiming her application of the factors this evidence); *see also* Carroll Cert., Exhibit B, Hutfless Dep. at 160:16-161:22. However, her use of the Bradford-Hill factors is flawed because, just like the expert in *Zoloft*, she inconsistently applied this methodology.

A. Strength of Association

Strength of association refers to the effect estimate generated by epidemiological studies. This is reported as a hazard ratio, relative risk, or odds ratio depending on the study design. Such studies ask the question: does exposure to the chemical/drug in question produce a statistically significant increased risk (meaning an effect estimate greater than one) for the outcome of interest? Since sprue-like enteropathy did not exist as an entity before June 2012, epidemiologists conducting retrospective observational studies of health claims databases were not able to use sprue-like enteropathy as a study outcome. Indeed, to date, no diagnostic ICD code for sprue-like enteropathy associated with olmesartan exists.

Consequently, investigators who want to conduct epidemiological research to determine if olmesartan is associated with an increased risk for sprue-like enteropathy must use an endpoint that they believe is a reasonable surrogate. One such study is Padwal, et al. *Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus*, Hypertension. 2014; 63:977-83. Carroll Cert., Exhibit S ("*Padwal*"). The *Padwal* study used ICD codes for gastrointestinal-related hospital admissions and admissions related to non-infective enteritis and colitis to determine if they were associated with olmesartan use compared to other ARB drugs. The authors found no statistically significant differences between olmesartan and other ARB drugs for gastrointestinal-related hospital admissions or admissions related to non-infective enteritis and colitis. *Id.*

at 981, Table 3. Despite admitting that the *Padwal* study controlled for all known confounders and used a sophisticated mechanism for selecting study subjects (*i.e.*, propensity scoring) (Carroll Cert., Exhibit B, Hutfless Dep., at 328:21-329:3, 348:20-21), Dr. Hutfless nevertheless concluded that it "d[id] not contribute to the evidence" on general causation. *See* Carroll Cert., Exhibit A, Hutfless Rep. at 25; Exhibit B, Hutfless Dep., 321:10-322:20. She eliminated this study from her analysis because it did not specifically investigate sprue-like enteropathy (which cannot be investigated for the reasons explained above). *See id.* at 322:2-24.

Researchers at Columbia Medical Center – which included one of the plaintiffs' experts, Dr. Lebwohl – published a second epidemiological study in 2014. *See* Carroll Cert., Exhibit T, Ruby Greywoode, M.D., et al., Olmesartan, other anti-hypertensives, and chronic diarrhea among patients undergoing endoscopic procedures; a case-control study, MAYO CLIN PROC. 89(9): 1239–1243 (Sept. 2014) ("*Greywoode*"). This paper examined patients who presented with symptoms of diarrhea and underwent endoscopies or colonoscopies. The olmesartan-user population was compared to other patients using other ARB drugs who underwent similar procedures. These authors could not find a statistically significant increased risk of diarrhea in patients using olmesartan. But Dr. Hutfless again concluded that this study "does not contribute to the evidence" because it involved too few olmesartan users and failed "to account for confounding by co-

morbidities or other medications in the analysis." Carroll Cert., Exhibit A, Hutfless Rep. at 25.

Dr. Hutfless also failed to consider another large epidemiological study, an analysis performed by the FDA and referred to as the Mini-Sentinel. *See id.* at 119-143, Table 15. The study investigated the number of "celiac disease" events among new users of ARBs and three non-ARB hypertension medicines for the time period 1/1/07 through 12/31/11. The mini-sentinel database contains health claims and administrative data from some of the largest healthcare systems in the United States – including Aetna, Kaiser, and Humana – involving more than 140 million individuals at 88 inpatient facilities. The use of these medicines represented more than 1.8 million person-years of use. *See generally* Carroll Cert., Exhibit U, 2013 FDA Mini-Sentinel Modular Program Report at Figure 1aiv (showing number of days at risk per medication). The analysis showed that not only were the occurrences of celiac disease among the ARBs very rare, the incidence rate for celiac disease among olmesartan users was not the highest among the ARBs. *See id.* at Figure 1bv (showing the number of new celiac disease events per 1 million days at risk for all ARBs, wherein other medications had higher rates than olmesartan). Despite Dr. Hutfless's claim that celiac disease is an appropriate surrogate endpoint to study (Carroll Cert., Exhibit A, Hutfless Rep., at 17; Exhibit B, Hutfless Dep. at 55:11-19)**,** she failed to even consider this study in

her analysis.

In comparison, the one study that Dr. Hutfless considered to be reliable reported a statistically significant increased risk for the discharge diagnosis of malabsorption. *See* Carroll Cert., Exhibit V, Mickael Basson, et al., Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study, Gut 2015;0:1-6, doi:10.1136/gutjnl-2015-309690 ("*Basson*"). Malabsorption, unlike the *Padwal* endpoint of non-infectious gastrointestinal disorders, can be caused by a number of different conditions having nothing to do with the gastrointestinal tract, such as cancer. *See, e.g.*, Carroll Cert., Exhibit W, Blaauw R., Ph.D., *Malabsorption: causes, consequences, diagnosis and treatment,* S AFR J CLIN NUTR 24(3); 125-27 (2011) (listing chronic pancreatitis, cystic fibrosis and pancreatic cancer as potential causes for malabsorption). However, Dr. Hutfless embraced the *Basson* paper even though it did not study "olmesartan induced enteropathy" and its endpoint would include many conditions unrelated to sprue-like enteropathy. Moreover, the *Basson* paper reported a statistically significant elevated risk for celiac disease among French citizens taking olmesartan. Yet Dr. Hutfless agreed that olmesartan does not cause celiac disease. Carroll Cert., Exhibit B, Hutfless Dep. at 246:16-247:1. Dr. Hutfless also admitted that the *Basson* investigators did not control for drugs that could cause or cure enteropathy. *Id.* at 262:23-263:8. Thus, contrary to the stated

reason for her disregarding the *Greywoode* study (*i.e.*, control for potential confounders), she embraced the results of the *Basson* study.

Dr. Hutfless also categorically dismissed both randomized clinical trials DSI conducted to examine olmesartan, trials in which the duration of drug use was nearly equal to the mean latency of 3.1 years reported in the 2012 Mayo Clinic paper. The largest and first of these clinical trials to be published was the ROADMAP study (the other, smaller study was ORIENT). The average duration of drug or placebo use in this study involving 4,447 subjects was 3.2 years. The results of the ROADMAP primary and secondary pre-specified endpoints were reported in the New England Journal of Medicine. *See* Carroll Cert., Exhibit X, "*Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes*" NEJM 364: 907-17 (2011).

Slightly more than a year later, after the Mayo Clinic published their paper on sprue-like enteropathy, the principal investigator for the ROADMAP study (Dr. Haller) and a colleague reviewed the gastrointestinal adverse event data from ROADMAP. Drs. Haller and Menne published the results of their review in a letter to the editor of the journal that published the 2012 Mayo Clinic paper. *See* Carroll Cert., Exhibit Y. They reported 78 intestinal associated adverse events among olmesartan users and 94 among those receiving placebo, and 127 adverse events of abdominal discomfort among olmesartan users and 125 among placebo

patients. *Id.* While acknowledging the possibility that sprue-like enteropathy may be so rare that it did not appear in this large, randomized clinical trial, the authors noted that their study did not reflect the clinical picture offered by the 2012 Mayo Clinic paper.

Rather than incorporating the ROADMAP data into her Bradford Hill analysis, Dr. Hutfless rejected the data in its entirety. Dr. Hutfless decided that the randomized trials involving olmesartan were irrelevant for two reasons. First, she claimed that the publications reporting on the clinical trials purportedly "did not report on gastrointestinal events . . ." or did not specify what threshold they used for reporting those adverse events. Second, for those that did report gastrointestinal adverse events, she decided that the trials were not structured to capture the "constellation of symptoms" related to "olmesartan induced enteropathy." Therefore, she concluded that the clinical trials "did not contribute to the overall evidence." Carroll Cert., Exhibit A, Hutfless Rep., at 23-24; *see also* Exhibit B, Hutfless Dep., at 351:14-354:12.

Dr. Hutfless's dismissal of the clinical trials (regarded as the best quality of data) is inconsistent with how she treated the MedWatch reports (the lowest quality data). The fact that the eight MedWatch reports were missing important data relevant to individual causation did not lead Dr. Hutfless to reject this low quality data. Instead, she elevated the data – using it as the solitary foundation for her

general causation opinion. Yet, for the clinical trials, Dr. Hutfless disregarded all of this evidence – largely due to the fact that the trials did not specifically report on sprue-like enteropathy outcomes. If Dr. Hutfless were to be believed, a randomized double-blinded clinical study of 4,447 subjects – which lasted on average 3.2 years – is insufficient compared to the evidentiary weight and persuasiveness of eight MedWatch reports.

B. Biological Plausibility

The "biological plausibility" factors looks at whether there is a known mechanism of action. Carroll Cert., Exhibit A, Hutfless Rep., at 9. Specifically, biological plausibility goes to whether "the association between exposure and disease is reasonable, given what is known about the disease." *Schneck v. Int'l Business Corp.*, No. 92-4370 (GEB), 1996 WL 8857589, at *17 (D.N.J. June 25, 1996), Carroll Cert., Exhibit FF. Dr. Hutfless purports to demonstrate "biological plausibility" by relying on two mechanistic papers, while readily admitting that she lacks the qualifications to interpret these papers. However, the methodological flaw in Dr. Hutfless's treatment of biologic plausibility is not her admission that she is not an expert in this area. Rather, it is her practice of cherry-picking data that supports her opinion and ignoring completely data of which she was aware before writing her report, but that is inconsistent with her opinion.

For example, her report states that the 2015 *de Araujo* paper stands for the

proposition that "olmesartan-induced enteropathy" exists in rats. *See* Carroll Cert., Exhibit A, Hutfless Rep., at 9, citing de Araújo AA, et al. *In a methotrexate-induced model of intestinal mucositis, Olmesartan reduced inflammation and induced enteropathy characterized by severe diarrhea, weight loss, and reduced sucrose activity*, Biol Pharm Bull. 2015; 38(5):746-52. doi: 10.1248/bpb.b14-00847 PubMed PMID: 25947920 ("*de Araujo* 2015"), Carroll Cert., Exhibit Z; *see also* Hutfless Dep., Exhibit B, 369:16-370:3, 373:24-374:2 (stating that the *de Araujo* paper stood for the "plausibility" Bradford-Hill factor).

But in 2014, the same group of investigators who published the 2015 paper published the results of a larger – but identical – rat study in which they concluded that olmesartan had an anti-inflammatory effect in the small intestine. Carroll Cert., Exhibit AA, Araujo Junior, et al., *Olmesartan Decreased Levels of IL-1b and TNF-a, Down-Regulated MMP-2, MMP-9,COX-2, RANK/RANKL and Up-Regulated SOCs-1in an Intestinal Mucositis Model*. PLoS ONE 9(12): e114923. doi:10.1371/journal.pone.0114923 ("2014 *de Araujo*"). Such a conclusion, Dr. Hutfless conceded at her deposition, was inconsistent with her theory of general causation. Carroll Cert., Exhibit B, Hutfless Dep., at 377:15-23. Strangely enough, the *de Araujo* 2015 paper also reached the same conclusion that olmesartan has anti-inflammatory effects in the small intestine. However, in the discussion portion of the 2015 paper, the authors comment – without reference to

data – that olmesartan may have induced diarrhea in some of the rats.

Dr. Hutfless could not explain why the 2015 *de Araujo* paper reached a different conclusion from the 2014 paper published by the same authors. *Id.* at 377:15-23 ("Q. . . . When you read the 2014 paper, where you saw that the investigators reported that using olmesartan in that group of 80 rats reduced inflammation in the gut, did not cause it? . . . A. So their conclusion, yes, is about reducing inflammation, that is correct."). Dr. Hutfless's basis for concluding that the *de Araujo* 2015 paper demonstrated biologic plausibility was that she "trusts" the paper to be true because it was peer-reviewed. *Id.* at 381:2-23, 388:9-17. However, the 2014 paper was also peer-reviewed. That notwithstanding, Dr. Hutfless could not provide a scientific rationale for why she disregarded the 2014 paper – which was larger than the 2015 paper and produced data inconsistent with her general causation opinion.

Dr. Hutfless also relied on a second paper to support her conclusion that data exists to demonstrate biologic plausibility. This paper by Marietta, *et. al*, "Immunopathogenesis of Olmesartan-Associated Enteropathy." Aliment. Pharmacol. Ther. 42:1-12 (2015) ("*Marietta*"), was published by many of the same authors of the 2012 Mayo Clinic case series. Carroll Cert., Exhibit BB. As stated in their 2012 paper, the Mayo Clinic investigators hypothesized that olmesartan may cause enteropathy in people by suppressing levels of TGF beta. *Id.* at 1. This

intracellular protein helps to down regulate inflammation. In this study, which involved human small bowel tissue biopsied in individuals complaining of enteropathy, the Mayo Clinic researchers found that the evidence did not support their primary hypothesis. *Id.* at 1-2. They did, however, report an increase in a pro-inflammatory cytokine, IL-15, and CD8+ cells – both of which would be expected to be elevated in a person with enteropathy. *Id.* at 4-5.

When questioned about the quality of the experimental design and data in the *Marietta* study, Dr. Hutfless quickly explained that she lacked the skills and qualifications to interpret the paper and, thus, would have to rely upon the peer-review process. Carroll Cert., Exhibit B, Hutfless Dep., at 387:12-389:6.

Given her inability to interpret the literature upon which she relies and her failure to consider contrary literature, Dr. Hutfless failed to adequately address biological plausibility.

C. Specificity

Specificity refers to whether factors other than the exposure can produce the outcome in question. Dr. Hutfless's treatment of this Bradford-Hill factor again demonstrates her willingness to depart from sound methodology and behave more like a litigation advocate than a scientist.

Here, Dr. Hutfless did not conduct a systematic search for adverse events involving other ARBs and enteropathy, despite knowing such adverse events

existed. Dr. Hutfless opined that "Olmesartan is unique among the ARBs to cause enteropathy. There was no signal for the other ARBs identified in FAERS. . . ." Hutfless Rep., Exhibit A, at 8. However, Dr. Hutfless knew when she wrote her report that her statement was incorrect. Knowing this, she deliberately chose not to investigate (as the Cochrane method would require) whether the evidence supported the finding that other ARBs were associated with enteropathy. If such evidence exists, it argues against specificity.

On September 22, 2016, Dr. Hutfless sent her colleague, Dr. Leffler, an email to which she attached a published peer-reviewed case report by the Mayo Clinic investigators. This case report examined another ARB, Valsartan, and determined – using evidence of de-challenge and re-challenge – that Valsartan was associated with sprue-like enteropathy. *See* Carroll Cert., Exhibit CC. Dr. Leffler responded that the report was not unexpected. *Id.* Despite this knowledge, Dr. Hutfless inexplicably failed to do a literature search to see if other ARBs were associated with enteropathy. When pressed on why she failed to do such a systematic literature search, she responded that her report was about olmesartan only. Carroll Cert., Exhibit B, at 438:12-441:13. Consequently, she felt no need to investigate other ARBs. Her cavalier dismissal of the potential association of other ARBs with enteropathy, and the complication that might pose for fulfilling the Bradford-Hill criteria for specificity, does not reflect sound scientific methodology

for assessing general causation.

Dr. Hutfless's failure to appropriately consider and consistently apply the Bradford Hill factors show that her methodology is flawed. Her testimony on general causation should therefore be excluded.

CONCLUSION

For the foregoing reasons, defendants' motion should be granted, and the testimony of Dr. Susan Hutfless should be excluded.

Respectfully submitted,

s/ Susan M. Sharko

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